



Objectives

Ethambutol (EMB) is a bacteriostatic agent often included in first-line antitubercular treatment regimens with rifampicin, isoniazid and pyrazinamide [1]. The primary role of EMB is to protect against rifampicin resistance in the event of pre-existing resistance to isoniazid.

EMB has been reported to have high oral bioavailability (approximately 80%) and is eliminated mainly via renal filtration and active tubular secretion, with 50% to 70% of an oral dose recovered unchanged in the urine of subjects with normal renal function [2-5].

The aim of this study was to describe the population pharmacokinetics of EMB in South African tuberculosis patients including characterisation of inter-individual and inter-occasion variability and exploring the causes of this variability.

Methods

Patients and data collection

- Pharmacokinetic data were obtained from patients diagnosed with pulmonary tuberculosis receiving antitubercular medication in two studies performed at DP Marais SANTA Centre (DPM) and Brewelskloof Hospital (BH).
- Patients received EMB doses of 800, 1000, 1200 or 1500 mg *q.d.*, with drug holidays on Saturdays and Sunday at DPM.
- At DPM blood samples were collected over a two-week period on four occasions at least two weeks after the start of therapy. On each occasion three samples were taken at random times between 0 and 12 hours post-dose. At BH samples were drawn pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 and 8 hours post-dose on one occasion two months after admission.
- Plasma concentrations of EMB were determined using a validated HPLC-tandem mass spectrometric method [6].

Model development

- Population PK model developed in NONMEM VI (FOCE INTER) [7].
- Single and multi-compartmental models with first-order absorption and elimination were evaluated.
- Various absorption models were explored including the use of a lag time, transit compartments and dual absorption compartments.
- Allometric body weight on oral clearance and volume terms and HIV status on bioavailability was evaluated initially based on *a priori* knowledge.
- Covariate model for oral clearance was established using the *scm* procedure in PsN [8,9] and included all statistically significant relationships from the univariate testing. The data set was randomly split (stratified for location) in two data sets, whereof one was used for the forward step (including univariate testing) and the other for the backward step.

Model qualification

- A visual predictive check with population prediction correction (1000 replicates) was used to assess the capability of the model to reflect the observed data [8-10].
- Imprecision in parameter estimates was obtained by non-parametric bootstrapping (200 samples) using PsN [8,9].

Results

- The observed data stratified for study location are shown in Figure 1 and patient characteristics are shown in Table 1.
- A two-compartment model with one transit compartment prior to first-order absorption and elimination described the data (Table 2).
- Allometric body weight scaling reduced objective function value by 24 units. Presence of HIV was borderline statistically significant and decreased bioavailability by 16%.
- Univariate search identified age, serum creatinine (SCR), creatinine clearance (CLCR), log-transformed alkaline phosphatase (lnALP) and mean corpuscular volume ($p < 0.05$). Dose level and location were assessed but did not fall out in univariate search. Forward *scm* included age, SCR and lnALP in the full model but none remained following the backward deletion.
- Inter-occasion variability exceeded inter-individual variability for oral clearance (45 vs 16 % CV).
- Imprecision was high in the peripheral volume of distribution and for several variance terms.
- Reasonable predictive properties demonstrated (Figure 2), but absorption not completely characterised.

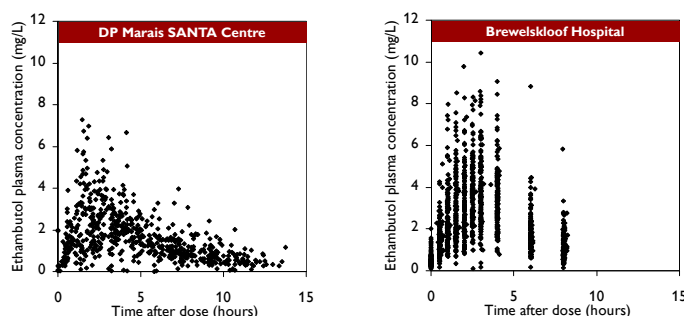


Figure 1. Observed ethambutol plasma concentrations versus time after dose. The seemingly different appearances in the data due to study location is mainly due to differences in dosing schedules and distribution of dose levels.

Table 1. Patient characteristics. Continuous variables shown as median (range) and categorical as number (%).

	DP Marais	Brewelskloof	All
Number of subjects	60	129	189
Number of samples	620	1260	1880
Age (years)	38 (18-64)	36 (16-72)	36 (16-72)
Body weight (kg)	52 (36-67)	46 (29-86)	47 (29-86)
Creatinine clearance (mL/min)	80 (51-150)	78 (23-128)	79 (23-150)
Sex	Male 45 (75) Female 15 (25)	Male 57 (44) Female 72 (56)	Male 101 (54) Female 87 (46)
HIV status	Positive 12 (20)	Positive 12 (9.3)	Positive 24 (12)

Table 2. Final population parameter estimates. Bootstrap estimates are presented as medians.

Parameter	Estimate NONMEM / Bootstrap	% Relative standard error ¹ NONMEM / Bootstrap
KA, absorption rate constant (h ⁻¹)	0.523 / 0.524	27 / 19
IIV on KA (CV)	0.43 / 0.45	85 / 58
MTT, mean transit time (h)	0.749 / 0.769	14 / 16
IIV on MTT (CV)	0.93 / 0.90	20 / 19
Presence of HIV on F, bioavailability (fractional change)	-0.167 / -0.165	34 / 34
CL/F, oral clearance (L/h)	40.3 / 40.2	3.4 / 8.1
IIV on CL (CV)	0.16 / 0.17	72 / 86
IOV on CL (CV)	0.45 / 0.44	35 / 110
V1/F, central volume of distribution (L)	96.2 / 97.8	40 / 27
V2/F, peripheral volume of distribution (L)	593 / 637 ²	18 / 87 ²
Q/F, inter-compartmental clearance (L/h)	34.9 / 33.6	7.4 / 9.0
Additive residual error (mg/L)	0.137 / 0.130	19 / 20
Proportional residual error (CV)	0.312 / 0.312	4.6 / 5.0

CV = coefficient of variation; IIV = inter-individual variability; IOV = inter-occasion variability
TVF = $1 \times (1 - 0.167^{FHV})$ HIV being 0 and 1 for negative and positive HIV status, respectively; TVCL = $40.3 \times (\text{body weight}/50)^{0.75}$; TVV1 = $96.2 \times (\text{body weight}/50)$; TVV2 = $593 \times (\text{body weight}/50)$; TVQ = $34.9 \times (\text{body weight}/50)^{0.75}$
¹Relative standard errors for IIV and IOV are related to the estimated variances; ²Two extreme bootstrap estimates (64 500 and 105 000) excluded, including these values yields bootstrap median (IQRSE) of 638 (550%).

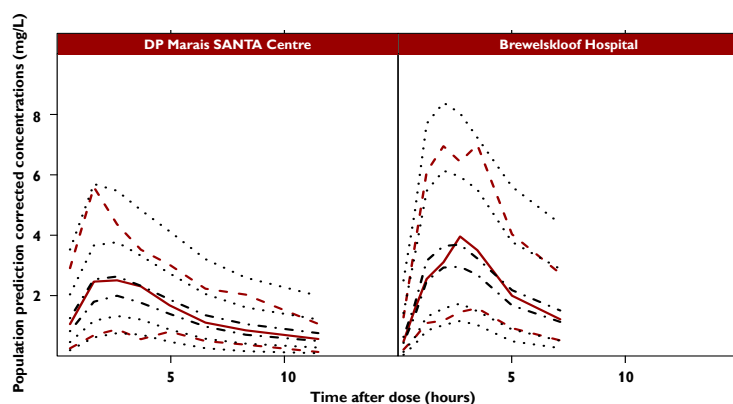


Figure 2. Results from visual predictive check applying population prediction correction. The prediction intervals (5th, 50th and 95th percentiles) of the observed data (red) are shown together with confidence intervals of the prediction intervals for the simulated prediction intervals.

Discussion and conclusions

- The estimated typical CL/F concur with Lee [2], but is roughly half CL/F reported by Peloquin and Zhu [11,12]. The latter may be partially attributable to differences in body weight between studies.
- The variable absorption of ethambutol has been hypothesised to be due to binding/chelation in the gastro-intestinal tract and suggested to be described by consecutive absorption processes [2,3].
- The decrease in bioavailability in presence of HIV is consistent with earlier findings [6,12].
- Renal function was not identified as a covariate, possibly due to that CLCR and body weight were positively correlated and most patients (86%) had CLCR ≥ 60 mL/min.
- The model will be used for predictions of systemic exposure in paediatric patients, which may need further elucidation of the influence of renal function.

References

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